M-11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 March 2000 (06.03.00)	
International application No. PCT/US99/10179	**Applicant's or agent's file reference** 1700PCT
International filing date (day/month/year) 10 May 1999 (10.05.99)	**Priority date** (day/month/year) 19 May 1998 (19.05.98)
Applicant MAY, Jesse, A. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 November 1999 (17.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Antonia Muller
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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PATENT COOPERATION TREATY

COPY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SALLY S. YEAGER
ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
MAIL CODE Q 148
FORT WORTH, TX 76134-2099

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	22 MAR 2000
Applicant's or agent's file reference 1700F US	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/10179	10 May 1999 (10.05.1999)	19 May 1998 (19.05.1998)

Applicant

ALCON LABORATORIES, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Richard L. Raymond Telephone No. (703) 308-1235

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1700PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/10179	International filing date *(day/month/year)* 10 May 1999 (10.05.1999)	Priority date *(day/month/year)* 19 May 1998 (19.05.1998)
International Patent Classification (IPC) or national classification and IPC IPC(7) A61K 31/443, 31/4965, 31/5415; C07D 241/02, 279/02, 401/12 and US Cl.: 514/226.5, 255, 323; 544/47, 398; 456/201		
Applicant ALCON LABORATORIES, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17 November 1999 (17.11.1999)	03 March 2000 (03.03.2000)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Richard L. Raymond Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/10179

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-24 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 25-62, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/10179

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-49	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-49	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-49	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)
Claims 1-49 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the present specific sulfonamides including the corresponding heterocyclic 1,2-thiazines. Industrial applicability exist because of the disclosed use in the treatment of sleeping disorders, depression and other psychiatric disorders.

---------- NEW CITATIONS ----------

NONE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1700PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/10179	International filing date *(day/month/year)* 10 May 1999 (10.05.1999)	Priority date *(day/month/year)* 19 May 1998 (19.05.1998)
International Patent Classification (IPC) or national classification and IPC IPC(7) A61K 31/443, 31/4965, 31/5415; C07D 241/02, 279/02, 401/12 and US Cl.: 514/226.5, 255, 323; 544/47, 398; 456/201		
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Date of submission of the demand 17 November 1999 (17.11.1999)	Date of completion of this report 03 March 2000 (03.03.2000)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Richard L. Raymond Telephone No. (703) 308-1235

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pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
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☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/10179

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1. STATEMENT

Novelty (N)	Claims 1-49	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-49	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-49	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)
Claims 1-49 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the present specific sulfonamides including the corresponding heterocyclic 1,2-thiazines. Industrial applicability exist because of the disclosed use in the treatment of sleeping disorders, depression and other psychiatric disorders.

---------- NEW CITATIONS ----------

NONE

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [7]:
A61K 31/443, 31/4965, 31/5415, C07D 241/02, 279/02, 401/12

A3

(11) International Publication Number: WO 99/59499

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60/086,002	19 May 1998 (19.05.98)	US

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(74) Common Representative: ALCON LABORATORIES, INC.; Yeager, Sally, S., R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States: AU, BR, CA, CN, JP, MX, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
16 March 2000 (16.03.00)

(54) Title: SEROTONERGIC $5HT_7$ RECEPTOR COMPOUNDS FOR TREATING OCULAR AND CNS DISORDERS

(57) Abstract

Compounds with $5HT_7$ receptor affinity (some of which are novel) useful for lowering IOP, improving blood flow to the optic nerve head and the retina, providing neuroprotection, and treating retinal diseases are disclosed. The Compounds are also useful for treating sleep disorders, depression, and other psychiatric disorders, such as, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension. Compositions and methods for their use are also disclosed.

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SEROTONERGIC $5HT_7$ RECEPTOR COMPOUNDS FOR TREATING OCULAR AND CNS DISORDERS

The present invention is directed to the use of compounds with serotonergic $5HT_7$ receptor affinity (Compound) (some of which are novel), to improve blood flow to the optic nerve head and the retina, provide neuroprotection, lower intraocular pressure (IOP), and treat retinal diseases, such as, glaucoma, age related macular degeneration (ARMD), optic neuritis, ischemic disorders, diabetic retinopathy, and retinal edema. The Compounds are also useful for treating sleep disorders, depression, and other psychiatric disorders, such as, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension.

Background of the Invention

Serotonin (5-hydroxy tryptamine; 5HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion, *Pharmacol. Rev.*, 44:401-458, 1992; Hoyer et al., *Pharmacol. Rev.*, 46:157-203, 1994; Tobin et al., *J. Neurosci.*, 8:3713-3721, 1988].

5HT can interact with at least seven major 5HT receptors ($5HT_1$ - $5HT_7$) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer et al., *supra*; Martin et al., *Trends Pharmacol. Sci.*, 19:2-4, 1998]. Receptor subtypes within the $5HT_1$ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while $5HT_4$, $5HT_6$, and $5HT_7$ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5HT [Martin et al., *supra*]. The receptors in the $5HT_2$ family are positively coupled to phospholipase C (PLC) and thus generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5HT. The $5HT_3$ receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer et al., *supra*].

The human and animal $5HT_7$ receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen et al., *Trend Pharmacol. Sci.*, 18:104-107, 1997]. Recent studies have shown there to be four splice variants of the $5HT_7$ receptor [Heidmann et al., *J. Neurochem.*, 68:1372-1381, 1997]. It has been proposed that the $5HT_7$ receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen et al., *supra*]. In the periphery, stimulation of $5HT_7$ receptors results in relaxation of blood vessels and hence vasodilation [Eglen et al., *supra*]. Improving blood flow to the back of the eye, including the retina, the macula, and the optic nerve head is believed to be beneficial in the treatment of a number of retinal diseases, for example, glaucoma, ARMD, and diabetic retinopathy [Chiou, et al., *J. Ocular Pharmacol.* 9:13-24 (1993)].

Serotonergic nerves innervate the eye [Tobin et al., *J. Neurosci.*, 8:3713-3721, 1988] and 5HT has been found in the aqueous humor of human eyes [Martin et al., *Ophthalmol.*, 95:1221-1226, 1988]. In addition, receptor binding sites for [^{3}H]5HT have been demonstrated and pharmacologically characterized in the iris-ciliary body (ICB) of rabbits [Mallorga and Sugrue, *Curr. Eye Res.*, 6:527-532, 1987 and Chidlow et al., *Invest. Ophthalmol. Vis. Sci.*, 36:2238-2245, 1995]. These 5HT binding sites have been shown to be functionally coupled to second messenger generation in rabbits [Tobin and Osborne, *J. Neurochem.*, 53:686-601, 1989 and Tobin et al., *J. Neurosci, supra*]. In the human ICB these binding sites are characterized as $5HT_{1A}$ and $5HT_2$ receptors [Barnet and Osborne, *Exp. Eye Res.*, 57:209-216, 1993]. In addition, the presence of mRNAs for $5HT_{1a}$ and $5HT_7$ receptors in the rabbit ICB have been reported [Chidlow et al., *Invest. Ophthalmol. Vis. Sci., supra* and Osborne and Chidlow, *Ophthalmologica*, 210:308-314, 1996]. The precise functions of these receptors in the eye are unknown, especially the $5HT_7$ subtype(s).

5HT or 5-carboxamidotryptamine (5-CT) topically applied to the rabbit eye raise intraocular pressure in the anterior chamber of the eye [Meyer-Bothling et al., *Invest. Ophthalmol. Vis. Sci.*, 34:3035-3042, 1993]. By contrast, it has been shown that topically applied 5HT lowers IOP [Krootila et al., *J. Ocular Pharmacol.*, 3:279-290, 1987 (intracamerally 5HT raised IOP and caused breakdown of the blood-aqueous barrier)]. In addition, the 5HT uptake inhibitor, fluoxetine (Prozac®), also raises IOP in human subjects

upon oral administration [Costagliola et al., *Br. J. Ophthalmol.*, 80:678, 1996] and may cause glaucoma [Ahmad, *Ann. Pharmacother.*, 25:436, 1992]. However, the 5HT receptor subtype(s) involved in the IOP-elevating effects of 5HT, 5-CT and fluoxetine are unknown.

Studies conducted in rabbits with 8-hydroxy DPAT and MKC-242 ($5HT_{1A}$ agonists) have shown these compounds lower IOP [Osborne and Chidlow, *Ophthalmologica*, 210:308-319, 1996, and EP 0771563-A2]. In addition, 5-methylurapidil ($5HT_{1A}$ agonist) lowered IOP in glaucomatous monkeys [Wang, et al., *Curr. Eye Res.*, 16:679-775, 1997]. Both MKC-242 and 5-methylurapidil are relatively potent $\alpha 1$ receptor antagonists ($\alpha 1$ antagonists are known to lower IOP in rabbits, monkeys, and man). The mechanism of action for lowering IOP by 5-methylurapidil has been attributed to its $\alpha 1$ antagonist activity and not its $5HT_{1A}$ agonist activity [Wang, et al., *Invest. Ophthal. Vis. Sci.*, 39(Suppl):2236-488, 1998]. U.S. Patent No. 5,693,654, discloses $5HT_1$ receptor agonists for lowering IOP. WO92/20333 discloses certain $5HT_{1A}$ agonists for the treatment of glaucoma.

Methysergide ($5HT_2$ antagonist) lowered IOP in rabbits [Krootila, et al., *Esp. Eye Res., supra*]. Ketanserin ($5HT_{2A/C}$ antagonist), also with significant $\alpha 1$ antagonist activity, lowers IOP in rabbits and man [Chan, et al., *J. Ocular Pharmacol.*, 1:137-147, 1985 and Costagliola, et al., *Ex. Eye Res.*, 52:507-510, 1991]. Saprogrelate ($5HT_{2A}$ antagonist) lowers IOP in rabbits and in man when dosed topically or orally [Mano, et al., *Invest. Ophthal. Vis. Sci.*, 36(Suppl):3322-309, 1995, and Takenaka, et al., *Invest Ophthal. Vis. Sci.*, 36(Suppl):3390-377, 1995]. EP 522226 and U.S. Patent No. 5,290,781 disclose the use of ketanserin and its derivatives for treating ocular hypertension. U.S. Patent Nos. 5,290,781 and 5,106,555 discloses the use of certain $5HT_2$ antagonists for lowering IOP. U.S. Patent No. 5,652,272 discloses saprogrelate for reducing IOP. U.S. Patent No. 5,538,974 discloses opthalmic compositions of certain $5HT_2$ antagonists for lowering IOP.

U.S. Patent No. 5,011,846 discloses certain $5HT_3$ receptor antagonists for treating glaucoma.

WO 97/17345 discloses that particular compounds with $5HT_4$ serotonergic receptor agonist or antagonist activity are useful for treating psychiatric, gastrointestinal, lower urinary, and cardiovascular disorders. The publication mentions the compounds may also be useful for glaucoma.

As evidenced by the previous discussion, it is not clear which serotonergic receptor activity is responsible for lowering IOP. Moreover, a number of these compounds are known to have activity at other receptors which are known to be involved in lowering IOP. Furthermore, it has not been cleared which receptor(s) might be responsible for increasing blood flow and providing neuroprotection in the eye.

Summary of the Invention

The present invention is directed to Compounds, some of which are novel, that have $5HT_7$ receptor affinity, and the use of compounds with $5HT_7$ receptor affinity to lower IOP, improve blood flow to the optic nerve head and the retina, provide neuroprotection, and control damage associated with diseases, such as, glaucoma, ARMD, optic neuritis, ischemic disorders, and retinal edema by functioning as neuroprotectants. Compositions of the compounds are contemplated for such uses. The Compounds are also useful for treating sleep disorders, depression, and other psychiatric disorders, such as, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension.

Detailed Description Preferred Embodiments

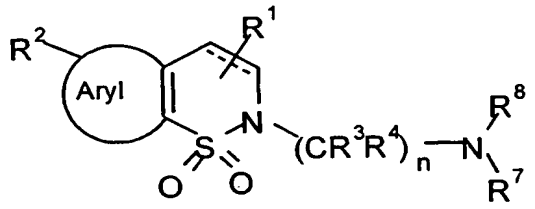
It has been unexpectedly discovered that $5HT_7$ receptors are present in the retina, choroid, and possibly the optic nerve head. Furthermore, sertonergic Compounds which possess a relatively high affinity (K_i = 0.01 - 200nM) for $5HT_7$ receptors effectively lower elevated IOP. It is believed that these Compounds can improve blood flow, and provide neuroprotection to the optic nerve head and the retina. The Compounds' (preferrably Compounds that are agonists or partial agonists) ability to improve blood flow to the optic nerve head and the retina and other characteristics are believed to render them

neuroprotective. The novel Compounds disclosed herein are also useful for treating sleep disorders, depression, and other psychiatric disorders.

Compounds found in the following applications are useful according to the present invention and are incorporated herein by reference: EP 738513-A1; WO 97/29097; WO 97/48681; WO 97/49695; and WO 98/00400. Specific Compounds include: LY-215840, SB-258719, and DR-4004.

The following novel Compounds and their pharmaceutically acceptable salts and solvates are useful for treating persons with the diseases and disorders previously described.

Formula I



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

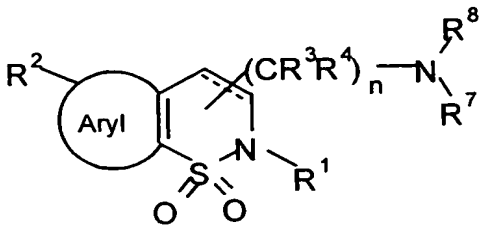
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine

or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2.

Formula II



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6

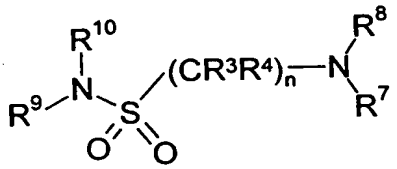
membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2.

Formula III



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

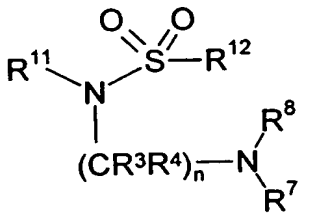
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4.

Formula IV



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

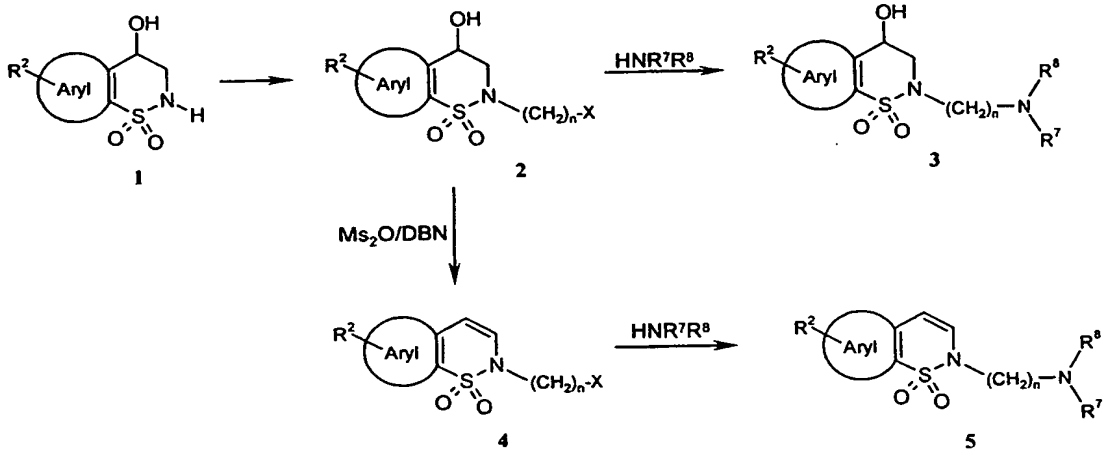
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4.

The compounds of the present invention can be prepared using chemical synthesis procedures herein described. The preferred method for preparing compounds of Formula I is illustrated in Scheme I. For example, the thiazine alcohols **1**, which can be prepared by methods described in U.S.Patents 5,344,929 and 5,470,973, or in *J. Org. Chem.* **31**, 162 (1966), can be selectively alkylated on the nitrogen atom at position two with, for example, a dihaloalkane using procedures known to the art to give **2**, where X is a halogen atom such as chlorine, bromine, or iodine. Compounds **2** can be treated with amines by known procedures to provide compounds of Formula I (**3**) where R^1 is hydroxyl, further these alcohols **3** can be treated with an alkylhalide to effect alkylation on oxygen to provide the ethers, R^1 is alkoxy. Alternately, **2** can be dehydrated by using methods described in U.S. Patent 5,538,966 to give compounds **4** which can be further reacted with amines to give compounds of Formula I where R^1 is hydrogen and the thiazine ring contains a double bond (**5**).

Scheme I

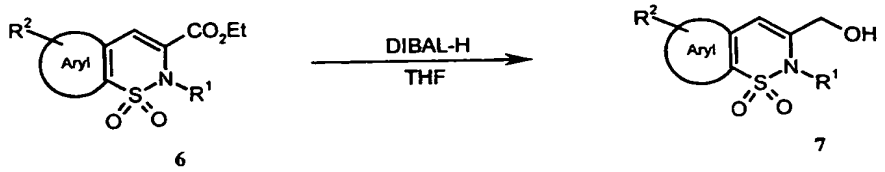


Procedures for preparing compounds of Formula II are illustrated in Scheme II. For example, the 3-hydroxymethyl thiazine compounds **7** can be prepared from the esters **6** by methods described in U.S. Patent 5,538,966 [Equation (a)]. Further, compounds **7** can be aminated using a variety of well known procedures, such as initial activation of the hydroxyl group by forming a sulfonate ester, followed by reaction of this intermediate with the desired primary or secondary amine to give compounds **8** of Formula II where R^3 and R^4 are hydrogen and n is 1 [Equation (b)]. Additionally, using **7** as an intermediate with which to initiate a suitable

homologation sequence, compounds of Formula II wherein R^3 and R^4 are hydrogen and n is 2 or 3 can be prepared; an example of such a homologation sequence employing 7 is illustrated in Equations (c) and (d), respectively.

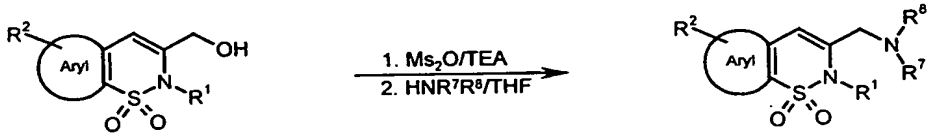
Scheme II

(a)



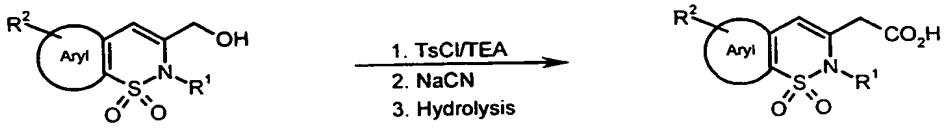
6 7

(b)

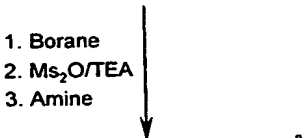


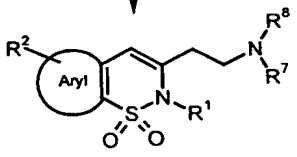
7 8

(c)



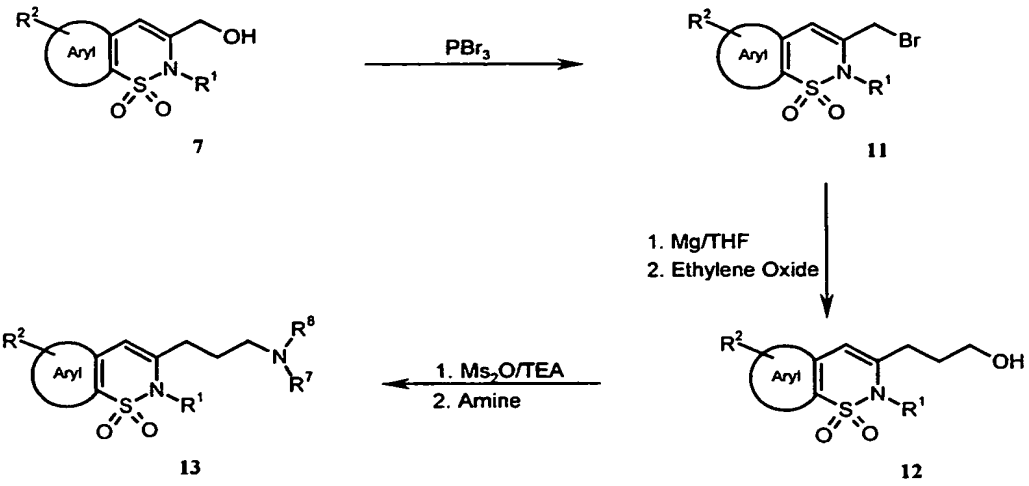
7 9





10

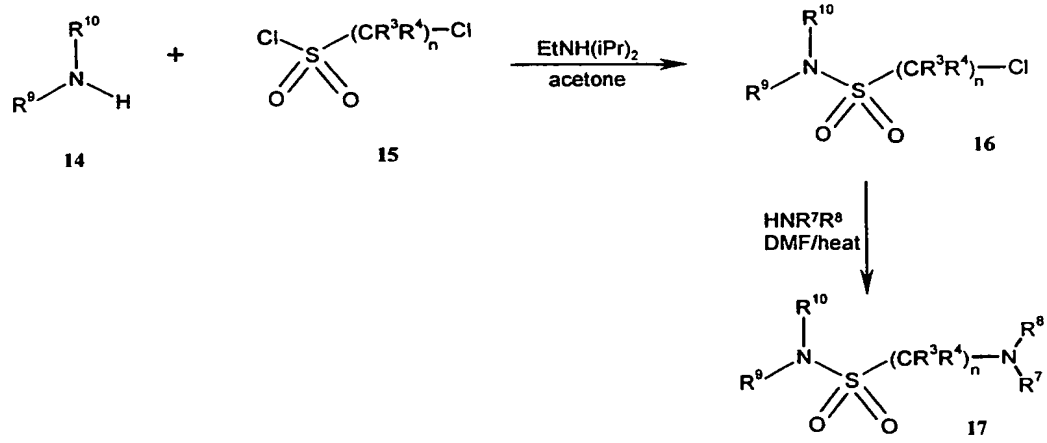
(d)



7 11 12 13

The preparation of compounds of Formula III can be readily accomplished by procedures herein described. For example, reaction of the desired amine **14** with the appropriate haloalkylsulfonyl chloride **15** in an inert solvent in the presence of a suitable base [see e.g., *J. Med. Chem.* **40**, 3217 (1997)] to give the haloalkylsulfonamide intermediate **16**. Subsequent reaction of **16** with the appropriate primary or secondary amine employing known procedures, provides compounds **17** of Formula III.

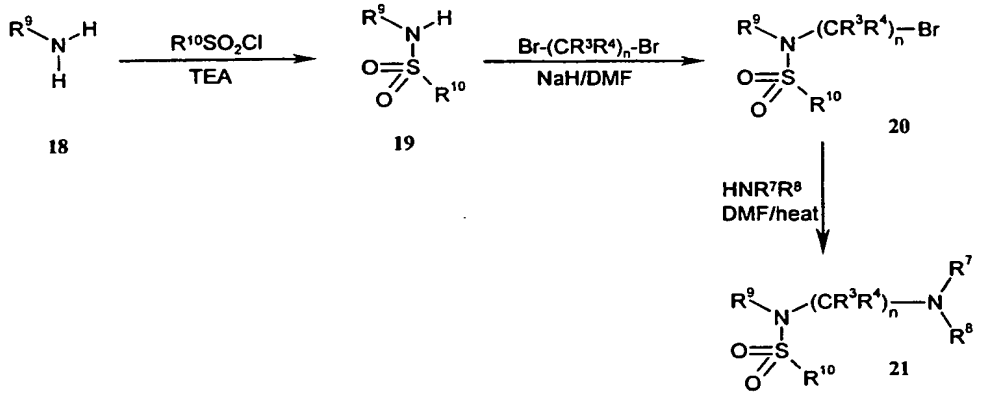
Scheme III



14 15 16 17

The preparation of compounds of Formula IV can be readily accomplished by procedures herein described. For example, reaction of the desired primary amine **18** with the appropriate sulfonyl chloride in an inert solvent in the presence of a suitable base provides the intermediate secondary sulfonamide **19** which can be alkylated by known procedures with the appropriately substituted alkyldibromide to give the haloalkylsulfonamide intermediate **20**. Subsequent reaction of **20** with the appropriate primary or secondary amine employing well known procedures provides compounds **21** of Formula IV.

Scheme IV



It is evident that some of the Compounds of Formula I - IV will include asymmetric atoms, all enantiomers and diastereomers are contemplated.

The term heteroaromatic ring refers to thiophene, furan, pyrrole, pyridine, pyrimidine, pyridazine and pyrazine.

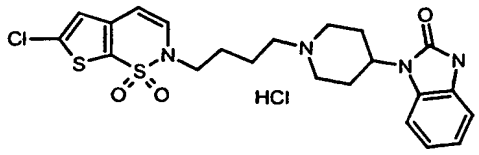
The Compounds can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant). The Compounds are preferrably incorporated into topical ophthalmic formulations for delivery to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic

suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated. The Compounds can be formulated for systemic (e.g. oral, I.V., I.M., subcutaneous) delivery according to methods known to one skilled in the art. For systemic delivery the Compounds are delivered at concentrations of 0.005 - 1000 mg. per dose, preferrably 0.05 - 20.0, most preferrably 0.2 - 5 mg. per dose. The Compounds will be dosed 1-4 times per day according to the discretion of a skilled clinician.

For ophthalmic medications the Compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The Compounds will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician. The preferred Compounds are those set forth in Examples 1, 1.1, 1.2, 1.6, 1.8, 2.3, 2.7, 2.10, 2.1, 2.4, 3, 3.1, 3.11, 3.5, and 3.10.

Example 1

6-Chloro-2-[4-[4-(2*H*-benzimidazo-2-oxo-1-yl)piperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide Hydrochloride



Step 1. A solution 6-chloro-3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2-thiazine-4-ol 1,1-dioxide (9.0 g, 37.6 mmol) in dimethylformamide (200 mL, anhydrous) and sodium hydride (60% in oil, 1.66 g, 41.5 mmol) was reacted with 1,4-dibromobutane at 0°. The reaction was stirred in an ice bath for 30 min and then it was allowed to warm to room temperature and stir for three days. The mixture was poured into ice water (400 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with water (200 mL), brine (200 mL) and then were dried over magnesium sulfate and evaporated. The resulting residue was purified by silica gel flash chromatography with hexane/ethyl acetate (7:3) to give 6-chloro-3,4-dihydro-2-(4-bromobutyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-4-ol 1,1-dioxide as a colorless oil (10.62 g, 75%); the ^{1}H NMR was consistent with the structure.

Step 2. The product from Step 1 (10.6 g, 28.3 mmol) was dissolved in tetrahydrofuran (anhydrous, 400 mL) and treated with triethyl amine (9.88 mL, 70.9 mmol) and methane sulfonic anhydride (9.86 g, 56.6 mmol) at room temperature and stirred for one hour. The suspension was concentrated and taken up in dimethylformamide (anhydrous, 120 mL). This mixture was heated at 160° for 45 min. The reaction mixture was poured into ice water (300 ml) and extracted with dichloromethane (300 mL). The organic layer was washed with water (2 x 200 mL), dried over magnesium sulfate and evaporated to a brown oil. After silica flash chromatography with hexane/ethyl acetate 6-chloro-2-(4-bromobutyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide was obtained as a yellow oil (4.97 g, 49%); the ^{1}H NMR. was consistent with the structure.

Step 3. A solution of 4-(2*H*-benzimidazo-2-oxo-1-yl)piperidine (0.30 mmol) in DMF (1.6 mL, anhydrous) and triethyl amine (0.5 mL) was treated with the product of Step 2 (0.103 g,

0.29 mmol) and stirred at 70° for 20 hours and then at room temperature for two days. The reaction mixture was diluted with ethyl acetate (3 mL) and water (4 mL). Saturated sodium bicarbonate (1 mL) was added and the layers were mixed followed by removal of the aqueous layer. The organic layer was washed with water (6 mL) and evaporated to give a residue that was dissolved in ethanol and treated with 1 N hydrochloric acid in ether. After evaporation the desired product was obtained as a white solid (69.2 mg, 45%): ^{1}H NMR and MS (M + H 493) were consistent with the structure.

By following the procedures of Example 1, but replacing 4-(2*H*-benzimidazo-2-oxo-1-yl)piperidine in Step 3 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

1. 6-Chloro-2-[4-(4-phenylpiperazin-1-yl)butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
2. 6-Chloro-2-[4-[4-(2-fluorophenyl)piperazin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
3. 6-Chloro-2-[4-[4-hydroxy-4-(4-chlorophenyl)piperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
4. 6-Chloro-2-[4-[4-hydroxypiperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride.

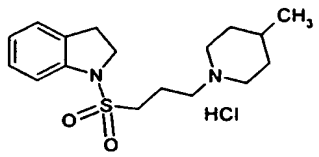
By following the procedures of Example 1, but replacing the 1,4-dibromobutane in Step 1 with 1,3-dibromopentane and 4-(2*H*-benzimidazo-2-oxo-1-yl)piperidine in Step 3 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

5. 6-Chloro-2-[3-[4-phenylpiperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
6. 6-Chloro-2-[3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;

7. 6-Chloro-2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
8. 6-Chloro-2-[3-[4-(2*H*-benzimidazol-2-oxo)piperidin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride.

Example 2

3-(4-Methylpiperidin-1-yl)propylsulfonyl-2,3-dihydro-1*H*-indole Hydrochloride



Step 1. To a solution of indoline (4.00 g, 33.6 mmol) in 100 mL of acetone at 0°C was added 3-chloropropanesulfonyl chloride (5.95 g, 33.6 mmol) with stirring. A solid precipitated from the solution. Diisopropylethylamine (4.33 g, 33.6 mmol) was added in two portions and the reaction mixture became a homogenous solution. The mixture was stirred for 30 min, warmed to ambient temperature, and evaporated to dryness. The crude mixture was combined with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate (2 x 100 mL). Chromatography on silica (10% to 25% ethyl acetate/hexane) gave an oil which solidified on standing (7.68 g, 77%, mp 53-53 °C).

Step 2. A mixture of the product of Step 1 (200 mg, 0.77 mmol) and 0.5 M solution of 4-methylpiperidine (4 mL, 2.0 mmol) was heated at 35 °C for 60 h. The reaction mixture was combined with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate (2 x 10 mL). The extracts were dried and evaporated to dryness. The crude product was filtered though a short silica column and treated with a 1.0 M solution of hydrogen chloride gas in ether. The solid was filtered and dried to give the hydrochloride salt (220 mg, 80 %): MS(ES) 323 (M+H).

By following the procedures of Example 2, but replacing 4-methylpiperidine in Step 2 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

1. 3-[4-(3-Chlorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
2. 3-(3-Methylpiperidin-1-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;
3. 3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;
4. 3-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
5. 3-(4-Phenylpiperazin-1-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;
6. 3-[4-(2-Fluorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
7. 3-[4-(2-Methoxyphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
8. 3-[4-(4-Methoxyphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
9. 3-[4-(2-Chlorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole.

By following the procedures of Example 2, but replacing the indoline in Step 1 with *N*-methylaniline and the 4-methylpiperidine in Step 2 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

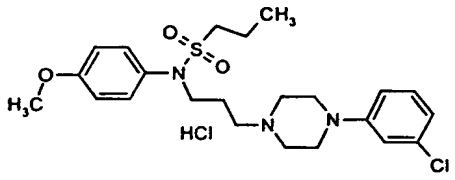
10. 3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-*N*-methyl-*N*-phenyl-propylsulfonamide;
11. *N*-Methyl-*N*-phenyl-3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propylsulfonamide;
12. *N*-Methyl-*N*-phenyl-3-(4-phenylpiperazin-1-yl)propylsulfonamide;
13. 3-[4-(2-Fluorophenyl)piperazin-1-yl]- *N*-methyl-*N*-phenyl-propylsulfonamide;
14. *N*-Methyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-*N*-phenyl-propylsulfonamide;
15. 3-[4-(2-Chlorophenyl)piperazin-1-yl]- *N*-methyl-*N*-phenyl-propylsulfonamide

By following the procedures of Example 2, but replacing the 3-chloropropanesulfonyl chloride in Step 1 with 2-chloroethanesulfonyl chloride and the 4-methylpiperidine in Step 2 with 3-methylpiperidine, the following compound was prepared. The ^{1}H NMR spectrum and the mass spectrum for this compound were consistent with the assigned structure.

16. 2-(3-Methylpiperidin-1-yl)ethylsulfonyl-2,3-dihydro-1*H*-indole.

Example 3

N-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide Hydrochloride



Step 1. To a solution of *p*-anisidine (6.00 g, 48.7 mmol) and triethylamine (5.91 g, 58.4 mmol) in methylene chloride (200 mL) at 0°C was added propylsulfonyl chloride (7.64 g, 53.6 mmol) with stirring under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed with a saturated aqueous solution of sodium bicarbonate (100 mL), water, and dried over magnesium sulfate. The organic layer was evaporated to give an oil that was mixed with a solution of hexane and ethyl acetate (3:1) to afford a crystalline solid (7.97 g). The mother liquid was chromatographed on silica (hexane/ethyl acetate, 4:1) to give a solid (2.27 g, 92%): mp 72°C; MS(-ES) 228 (M-H).

Step 2. To the product of Step 1 (3.50 g, 15.3 mmol) in anhydrous dimethylformamide (80 mL) at 0°C was added sodium hydride (60 % suspension in mineral oil, 0.672 g, 16.8 mmol) under a nitrogen atmosphere. The suspension was stirred for 30 min and 1,3-dibromopropane (9.27 g, 45.9 mmol) was added over 1 min. The reaction was stirred for 3 h, mixed with a saturated aqueous solution of sodium bicarbonate (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried and evaporated to dryness. Chromatography on silica (20% ethyl acetate in hexane) gave a colorless oil (4.33 g, 81%): MS(+ES) 352 (M+H).

Step 3. To a solution of the product of Step 2 (0.175 g, 0.50 mmol) in anhydrous dimethylformamide (1 mL) was added a 0.5 M solution of 1-(3-chlorophenyl)piperazine in dimethylformamide (1.1 mL, 0.55 mmol) and triethylamine (0.20 mL); this mixture was heated at 60°C for 18 h. The cooled reaction mixture was extracted with ethyl acetate (2 x 1 mL) and the combined extracts were washed with a saturated aqueous solution of sodium

bicarbonate, dried and evaporated to an oil which was treated with a 1.0 M solution of hydrogen chloride gas in ether to give the corresponding salt (0.11 g, 44%): MS(ES) 466 (M+).

By following the procedures of Example 3, but replacing 1-(3-chlorophenyl)piperazine in Step 3 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

1. *N*-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
2. *N*-[3-(3-Hydroxymethylpiperidin-1-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
3. *N*-(4-Methoxyphenyl)-*N*-[3-(morpholin-4-yl)propyl]-propanesulfonamide;
4. *N*-(4-Methoxyphenyl)-*N*-[3-(2-methylpiperidin-1-yl)propyl]-propanesulfonamide;
5. *N*-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
6. *N*-(4-Methoxyphenyl)-*N*-[3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propyl]-propanesulfonamide;
7. *N*-[3-(4-phenylpiperazin-1-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
8. *N*-[3-[4-(2-Fluorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
9. *N*-[3-[4-(4-Methoxyphenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
10. *N*-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
11. *N*-[3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
12. *N*-[3-[4-(2*H*-Benzimidazo-2-oxo-1-yl)piperidin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide.

By following the procedures of Example 3, but replacing the 1,3-dibromopropane in Step 2 with 1,4-dibromobutane and the 1-(3-chlorophenyl)piperazine in Step 3 with 1,2,3,4-

tetrahydroisoquinoline, the following compound was prepared. The ^{1}H NMR spectrum and the mass spectrum for this compound were consistent with the assigned structure.

13. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-*N*-(4-methoxyphenyl)-methanesulfonamide.

The following topical ophthalmic formulations are useful according to the present invention administered 1-4 times per day according to the discretion of a skilled clinician.

EXAMPLE 4

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 5

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Cremophor EL	0.1%
Tromethamine, USP, AR	0.64%
Mannitol, USP	3.0%
Boric acid, USP	0.3%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

EXAMPLE 6

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 7

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Hydroxypropyl-β-cyclodextrin	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 8

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Xanthan gum	0.5-6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 9

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 10

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Tyloxapol	0.2 – 4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 11

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

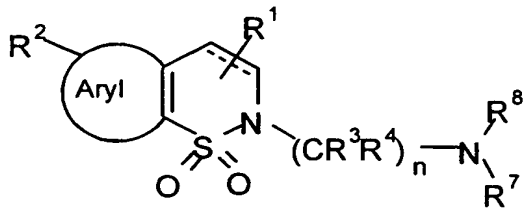
EXAMPLE 12

Formulation for Oral Administration

Tablet: 0.2 - 5 mg. of $5HT_7$ Compound with inactive ingredients such as cornstarch, lactose, colloidal silicon dioxide, microcrystalline cellulose, and magnesium sterate can be formulated according to procedures known to those skilled in the art of tablet formulation.

We Claim:

1. A compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

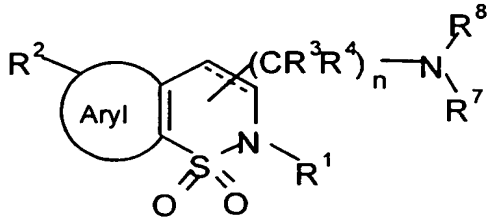
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

2. A compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted

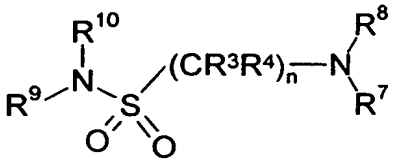
optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

3. A compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

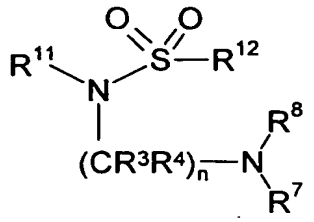
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

4. A Compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

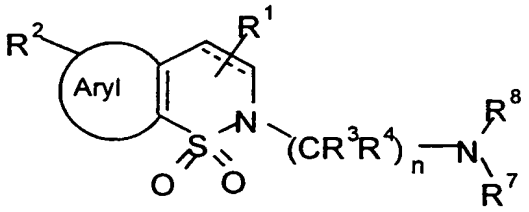
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

5. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

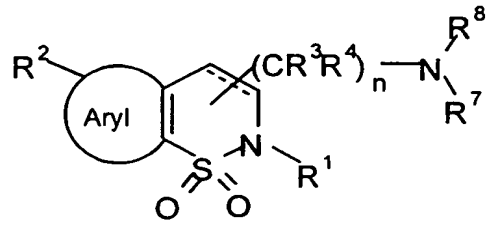
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

6. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or

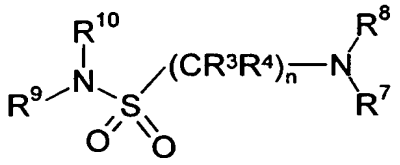
more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

7. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

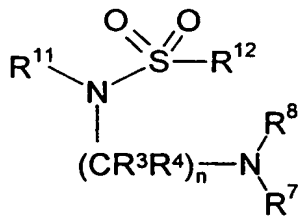
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

8. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

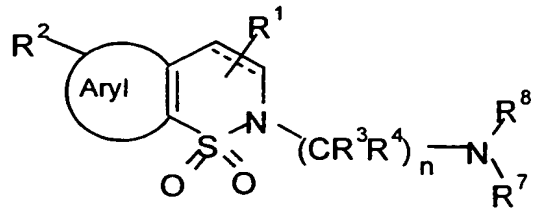
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

9. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

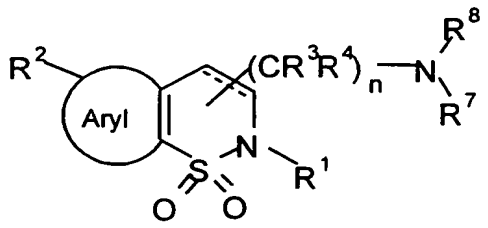
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

10. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine

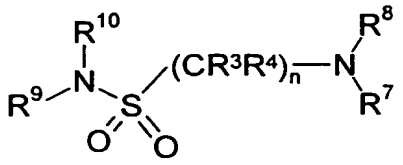
or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

11. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

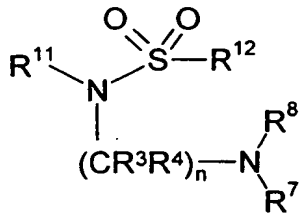
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

12. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

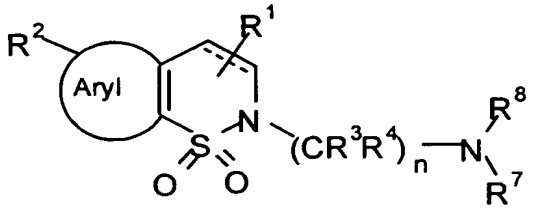
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

13. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2\ NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

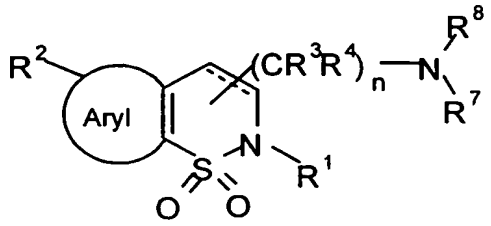
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

14. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2\ NR^5R^6$; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2\ NR^5R^6$; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2\ NR^5R^6$, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected

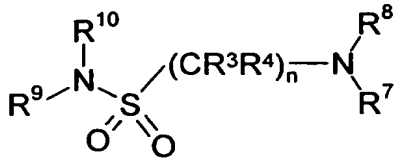
from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

15. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

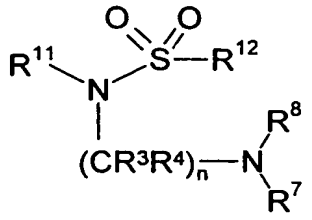
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

16. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

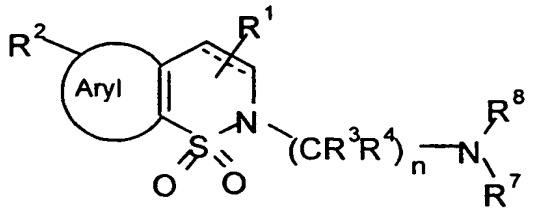
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

17. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

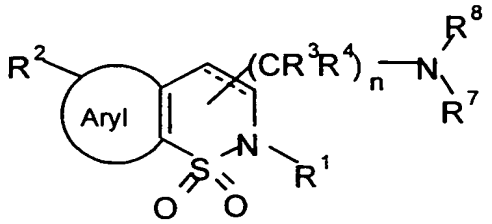
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

18. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or

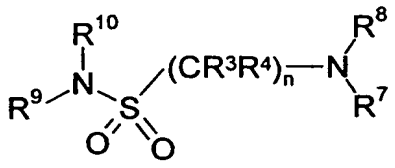
more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

19. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

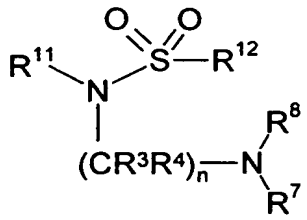
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

20. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

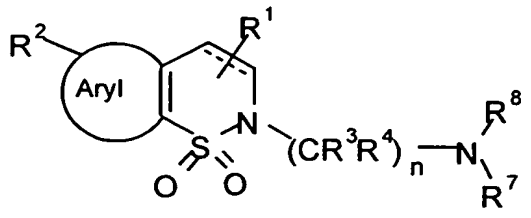
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

21. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

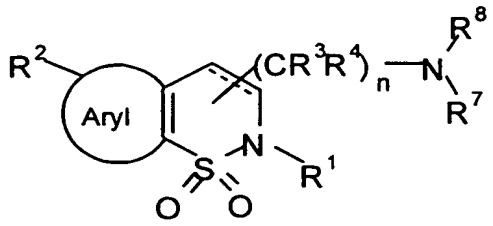
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

22. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

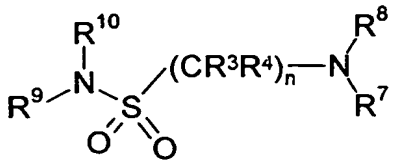
with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

23. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

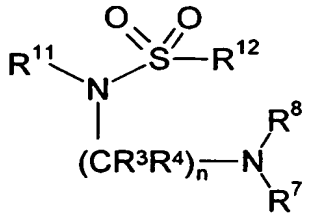
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

24. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a Compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

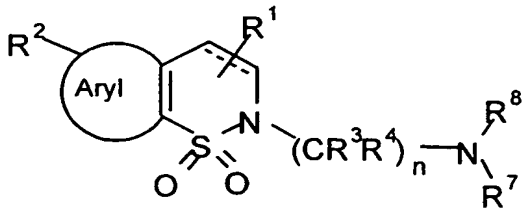
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

25. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

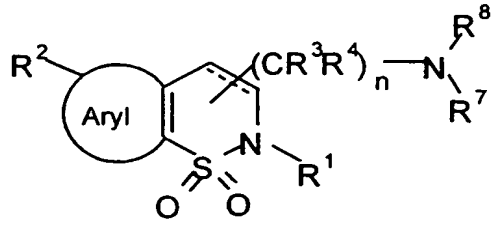
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

26. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

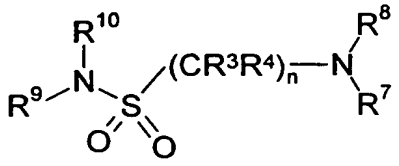
with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

27. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

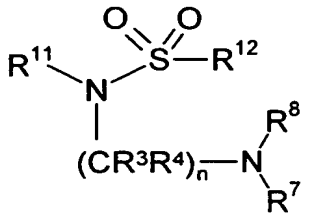
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

28. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

29. A method for improving blood flow to the optic nerve head or the retina which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

30. A composition for improving blood flow to the optic nerve head or the retina comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

31. A method for providing neuroprotection to the optic nerve head or the retina which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

32. A composition for providing neuroprotection to the optic nerve head or the retina comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

33. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

34. The method of Claim 1 wherein the retinal disease is selected from the group consisting of glaucoma, age related macular degeneration, optic neuritis, ischemic disorders, and retinal edema.

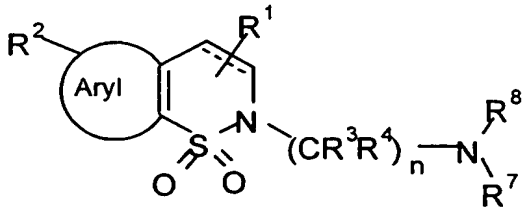
35. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

36. The composition of Claim 35 wherein the retinal diseases are selected from the group consisting of glaucoma, age related macular degeneration, optic neuritis, ischemic disorders, diabetic retinopathy, and retinal edema.

37. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

38. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

39. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, circadian rhythm disorders, and centrally and peripherally mediated hypertension, which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

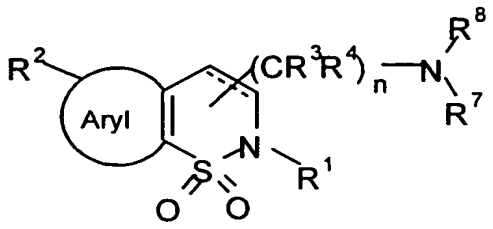
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

40. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythem disorders, and centrally and peripherally mediated hypertension which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

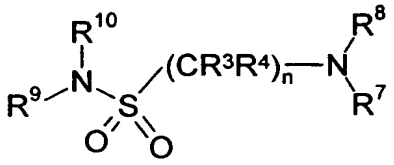
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

41. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, obsessive compulsive disorders, circadian rhythm disorders, and centrally and peripherally mediated hypertension which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

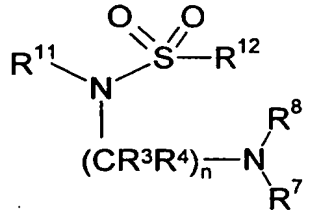
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

42. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

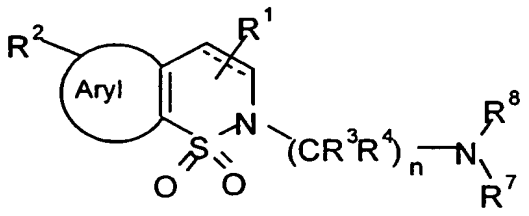
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

43. A composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2\ NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted

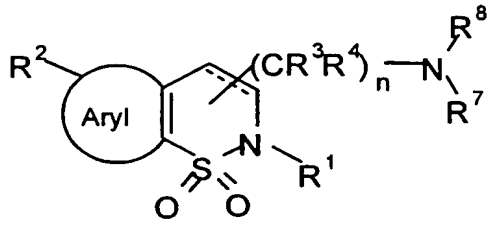
optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

44. A composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2NR^5R^6$; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2NR^5R^6$; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6

membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

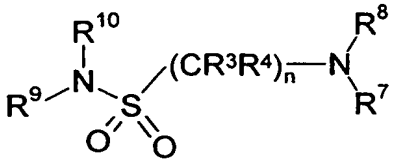
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

45. A composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

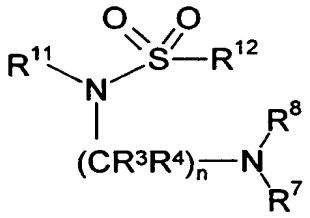
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

46. A composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

47. The Compound of Claim 1 selected from the group consisting of:

6-Chloro-2-[4-[4-(2*H*-benzimidazo-2-oxo-1-yl)piperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[4-(4-phenylpiperazin-1-yl)butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[4-[4-(2-fluorophenyl)piperazin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[3-[4-(2*H*-benzimidazol-2-oxo)piperidin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide.

48. The Compound of Claim 3 selected from the group consisting of:

3-[4-(3-Chlorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;

3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;

3-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;

3-[4-(2-Methoxyphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;

3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-*N*-methyl-*N*-phenyl-propylsulfonamide;

49. The Compound of Claim 4 selected from the group consisting of:

N-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/10179

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/443, 31/4965, 31/5415; C07D 241/02, 279/02, 401/12
US CL :514/226.5, 255, 323; 544/47, 398; 546/201
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/226.5, 255, 323; 544/47, 398; 546/201

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN/CAS, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,880,134 A (COHEN et al.) 09 March 1999, whole document.	1-49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 DECEMBER 1999	Date of mailing of the international search report 27 JAN 2000
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Form PCT/ISA/210 (second sheet)(July 1992)*